Application No. 10/070,302
Filed: May 1, 2002
TC Art Unit: 1641
Confirmation No.: 2837

REMARKS

Claims 1-28 were pending in the present application. Claims 2 and 13 are cancelled herein, without prejudice. Claims 1, 4, 9, 16, 19 and 27 are amended herein. Accordingly, claims 1, 3-12 and 14-28 will be pending upon entry of the instant amendments.

Support for the amended claims can be found throughout the specification and encompassed by the scope of the claims as originally filed. In particular, the amendment to the claims was made to more clearly define the present invention and in response to the claim objections and rejections under 35 U.S.C. §112, second paragraph, as further explained below. No new matter has been added.

Any amendments to the claims should in no way be construed as acquiescence to any of the Examiner's rejections and were done solely to expedite the prosecution of the application. Applicant reserves the right to pursue the claims as originally filed in this or a separate application(s).

Claim Rejections - 35 U.S.C. §112, 2nd ¶

Claims 1-28 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite.

Applicants amended the claims accordingly to address the Examiner's concerns with respect to the foregoing rejection.

With respect to claim 1, the following comments are provided for the specific concerns raised by the Examiner:

With regard to paragraphs 4)a) and 4)b) of the Office Action, the subject matter of the amended claim 1 is not restricted to the provision of a complete antibody but provides a "proteinaceous compound or functionally active derivative or part thereof" that

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is capable of binding a compound represented by formula (I). (*See*, for example, page 5, lines 12-17, of the specification.) This proteinaceous compound may be one or more polypeptides that comprises a binding site specific for the compound represented by formula (I) (*see*, page 5, lines 19-24, of the specification). Only the active portion of this proteinaceous compound binds to the compound of formula (I). Also described on page 7, lines 15-19, of the specification, examples of a "proteinaceous compound" may include "polyclonal, monoclonal or recombinant antibody." The compound of the present invention may contain only one (instead of two in a complete antibody) or more than two binding sites for the compound represented by formula (I) which may be achieved by techniques well known in the art, for example, recombinant nucleic acid technology in combination with translation and expression of the obtained genes and/or selection via display libraries, e.g., phage display (*see*, page 7, lines 8-13, of the specification). Therefore, it cannot be presumed that what is being claimed in claim 1 is an "antibody" per se. Additionally, for the purposes of providing a novel system for the reliable detection as well as the removal of all kinds of microcystin and nodularin congeners, especially from drinking water and other sources, it is not essential to provide complete antibodies directed to the compound capable of specifically binding to a compound represented by formula (I).

In paragraph 4)d) of the Office Action, the Examiner asserts that it is unclear how "the given definitions of R^1 and R^2 could be combined to form "a cyclic moiety…." Applicants submit that it is clear from the language in the claims that either "group R^1 represents a halogen atom, $-OSO_3$, -OR' or $-NR'_2$ and group R^2

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represents hydrogen, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, (C_1-C_4)acyl, (C_1-C_4)acylamino, (C_1-C_4)carboxyaminoacyl, glutamidyl, or 2-aminoproprionamidly" or "the groups R^1 and R^2 are connected to each other to form a cyclic moiety." An ordinary skilled artisan would know which groups would be appropriate to make a cyclic moiety. Reconsideration is respectfully requested.

With respect to paragraph 6) of the Office Action, Applicants have amended the claims to correct the typographical error to "acylamino," which is what was intended based on the specification and, in particular, Fig. 3.

Claim Rejections - 35 U.S.C. §112, 1st ¶

Claims 1-28 are rejected under 35 U.S.C. §112, first paragraph, for nonenabling "(C_1-C_4)aminoacyl." Applicants accordingly amended the claims to correctly recite them as "acylamino" as explained above.

Claims 1-28 are rejected under 35 U.S.C. §112, first paragraph, as being nonenabling for the preparation of immunogens using the other structures encompassed by formula (I) of claim 1.

Applicants respectfully traverse the foregoing rejection.

The provision of the compound claimed in claim 1 of the present invention, an attachment of an immunogenic carrier to a reactive functional moiety in formula (I) is not necessary. While having the property of antigenicity but not immunogenicity, free haptens can react with products of an immune response. Therefore, the provision of the compound according to claim 1 does not require the attachment of an immunogenic carrier.

Claims 11 and 21 are rejected under 35 U.S.C. §112, first paragraph, for lack of written description. The Examiner notes that it is unclear how "plastic supports" and "polyethylene glycol" could be used as carriers to prepare the immunogens of claim 11.

Applicants respectfully traverse the foregoing rejection.

Hapten-carrier conjugates are immunogenic molecules to which haptens have been covalently linked. The immunogenic molecule is called the carrier. Therefore, any polymeric carrier, including a plastic support and polyethyleneglycol, having immunogenicity can serve as a carrier. Immunogenicity can be enhanced, e.g., by coupling the polyethylene glycol-hapten complex to an immunogenic molecule.

Claim Rejections - 35 U.S.C. §102(b) and §103(a)

Claims 1-28 are rejected under 35 U.S.C. §103(a) as being obvious over Nagata et al. (*Natural Toxins* 3:78-86 (1995)) or An et al. (*Toxicon* 32(12):1495-1507 (1994)) in combination with Humphrey et al. (*JACS* 118:11759-11770 (1996)).

Claims 1-9 are rejected under 35 U.S.C. §102(b)/103(a) as being unpatentable over each of Nagata et al. or An et al.

Claims 10-28 are rejected under 35 U.S.C. §103(a) as being obvious over Nagata et al. or An et al.

Applicants respectfully traverse the foregoing rejections.

The presently claimed invention is directed to a compound comprising one or more polypeptides providing a binding site of a monoclonal, polyclonal or recombinant antibody or a functionally active derivative or part thereof capable of specifically binding

to a compound represented by formula (I), as further described above with respect to claim 1.

None of the cited publications discloses, either explicitly or implicitly, a compound having a binding site for a compound represented by formula (I) as defined in newly amended claim 1, i.e., the ADDA group or moiety. The antibodies disclosed in Nagata et al. and An et al. were all raised against complete microcystin-LR (MC-LR) molecules and not against the isolated ADDA group. As a consequence, each of the antibodies contains a binding site for an epitope which may overlap with the ADDA moiety but which also interacts with other groups present in complete MC-LR. The present invention is novel in that the proteinaceous compounds of the invention do not exhibit extreme variations in cross-reactivities whereas in the cited art, much variation is shown.

Nagata et al. reports extreme variations in cross-reactivity of anti-microcystin-LR monoclonal antibodies with various microcystin congeners and nodularin. The results indicate a range from less than 2 to 900% as shown in Table II (page 82) (*see also*, page 81, 2nd column, 1st paragraph). If the antibodies disclosed in Nagata et al. were specifically directed to the ADDA group, as is in the present invention, such variations would not have been observed. While the ADDA moiety may be part of the microcystin and nodularin toxins, the proteinaceous compounds of the present invention is plainly not the same or functionally equivalent to the antibodies in Nagata et al. since the reactivities are not the same. Nagata et al. fails to anticipate the each and every element of the claimed invention.

Moreover, Nagata et al. cannot teach or suggest the claimed invention. The Examiner asserts that Nagata et al. describes this "ADDA" moiety of microcystins as being "the key functional domain of the microcystins (page 84, first full paragraph)." However, based on its experimental data provided, this statement cannot be supported but is a mere assumption. It is explicitly stated in Nagata et al. that the alteration of the variable Arg residue in microcystin congeners reduces the ability of the monoclonal antibodies described in Nagata et al. to recognize microcytsin cyclic peptides with high specificity. Accordingly, in Nagata et al., the authors themselves admit that the described antibodies are not specifically directed to the ADDA group but recognize an epitope which includes the Arg residue present in complete MC-LR (*see* page 82, the paragraph preceding TABLE III, and page 84, left column). Based on these contradictory assertions, Nagata et al. cannot either teach or suggest the claimed invention since the present invention has better binding specificity and less cross-reactivity than those antibodies disclosed in Nagata et al.

Analogous to Nagata et al., An et al. also show variations ranging from 9 ([D-Asp^3]MCYST-LR) to 100% ([D-Glu-OCH$^6{}_3$]MYCST-LR, Table 1) with respect to various nodularin and microcystin congeners which contain the ADDA group. (*See*, page 1499, last paragraph of An et al.) Again, if the antibodies disclosed in this cited document was specifically directed to the ADDA group, such variations would not have been observed. The antibodies of An et al. were also raised against complete microcystin-LR (MC-LR) molecules and not against the isolated ADDA group. Each of the antibodies in An et al. also contain a binding site for an epitope which may overlap with the ADDA moiety but which also interacts

with the other groups present in MC-LR. An et al. cannot anticipate each and every element of the claimed invention.

An et al. also fails to teach or suggest the claimed invention. An et al. explicitly state that the Arg residue in microcystin congeners is essential for expressing the specificity of all antibodies used in this cited reference (*see*, page 1503, last paragraph). The present invention is distinguishable in that this is not the case.

Neither Nagata et al. nor An et al. teach or suggest providing a compound that is specifically directed to a compound of formula (I) as defined in the present claim 1. In particular, the subject matter of the present invention is based on a site-directed binding of the compound of new claim 1 of the present invention to the isolated ADDA moiety, in order to obtain a compound capable of binding with high specificity to all kinds of microcystin and nodularin congeners. In contrast to the present invention, the antibodies disclosed in the cited publications actually bind at least to some extent to different microcystin congeners but they seem to be the result of pure chance, since these antibodies were raised against complete MC-LR. As a consequence, the antibodies of Nagata et al. and An et al. display extreme variations in cross-reactivity with respect to different microcystin congeners.

Furthermore, an ordinary person skilled in the art would have no motivation to make a compound according to the presently claimed invention. The cited publications fail to teach or suggest a compound that displays better cross-reactivity across the broadest range of microcystin congeners. The present invention displays surprising properties where there is low

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variation in cross-reactivity across a very broad range of microcystin congeners as well as excellent quantification characteristics when tested in, e.g., a competitive ELISA (*cf.*, page 24, line 27, to page 25, line 10, and Fig. 5 of the specification). (*Nota bene:* Additional data showing low variation in cross-reactivity of microcystin congeners and nodularin using the compound of the present invention will be submitted in a separate declaration, which will be forthcoming shortly.)

Humphrey et al. fails to cure the deficiencies found in either Nagata et al. or An et al. Humphrey et al. only relates to the chemical synthesis and structure of MC-LA. This cited reference describes the total synthesis of a microcystin congener and is silent with regard to a compound providing a binding site thereto as claimed in the present invention. Either alone or in combination with Nagata et al. or An et al., Humphrey et al. fails to teach or suggest, let alone provide any requisite motivation, to come up with the presently claimed invention.

Applicants consider that claim 1 and its respective dependent claims as well as the other claims directed to claim 1 are novel and non-obvious over the cited references and respectfully request reconsideration and withdrawal of all of the foregoing rejections.

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CONCLUSION

Based on the foregoing, entry of the amendments and remarks presented herein, reconsideration and withdrawal of all the rejections and allowance of application with all pending claims are respectfully requested.

The Examiner is encouraged to telephone the undersigned attorney to discuss any matter that would expedite allowance of the present application.

Respectfully submitted,

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